

Relationship of miRNA-126 and miRNA-122 expression with type 2 diabetes mellitus and related glucose metabolism parameters: A systematic review and meta-analysis

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Abstract. There are increasing numbers of studies investigating the potential link between microRNAs (miRNAs) and type 2 diabetes mellitus (T2DM) risk. Based on the prior evidence and the differentially expressed candidate plasma exosome miRNAs in our established discovery study, the current meta-analysis studied miR-126 and miR-122 specifically. The purpose of the present study was to systematically and quantitatively evaluate the relationship of miR-126 and miR-122 expression level with T2DM risk as well as related glucose metabolism parameters. Moreover, the present study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA 2020 statement). PubMed, Embase, Web of Science, Cochrane and Chinese National Knowledge Infrastructure electronic databases were used to identify eligible original studies prior to May 3, 2022. The random-effects models were employed to explore the overall effect estimates [odds ratio (OR) and 95% confidence interval (CI), or correlation coefficient (r, 95% CI)].

The subgroup analyses were conducted to examine the potential sources of heterogeneity. The potential publication bias was assessed by the Begg's funnel plot and Egger's tests. A total of 46 articles were included in the present meta-analysis. The results revealed that higher exposure level of miR-126 was related to lower T2DM risk in 5 analytical epidemiological studies [OR=0.73, 95% CI: (0.55, 0.96)], lower fasting blood glucose (FBG) [N=22, r=-0.26, 95% CI: (-0.42, -0.10)], and lower homeostasis model assessment of insulin resistance (HOMA-IR) index [N=9, r=-0.28, 95% CI: (-0.52, -0.05)]. Besides, positive correlations were observed between miR-122 expression and FBG [N=10, r=0.34, 95% CI: (0.20, 0.48)], as well as HOMA-IR index [N=9, r=0.40, 95% CI: (0.16, 0.64)]. The relationship of miR-126 and miR-122 expression with T2DM risk and these glucose metabolism parameters may be influenced by study types, sample size, different source and mean age of participants. In conclusion, in the general healthy population, higher miR-126 expression was related to lower T2DM risk, FBG level and HOMA-IR index; higher miR-122 expression was closely correlated with higher FBG level and HOMA-IR index. These findings have notable clinical and public health implications for screening and control glucose metabolic disorders, insulin resistance and T2DM development.

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Abbreviations: T2DM, type 2 diabetes mellitus; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment of insulin resistance; miRNAs, microRNAs; OR, odds ratio; CI, confidence interval; RR, relative ratio; HR, hazard ratio; r, correlation coefficient; ZCOR, Fisher's z transformation of correlations; NOS, the Newcastle Ottawa Scale; SE, standard error; RT-qPCR, reverse transcription quantitative polymerase chain reaction; SD, standard deviation

Key words: miRNA-126, miRNA-122, type 2 diabetes mellitus, glucose metabolism parameters, meta-analysis

Introduction

As the fourth leading cause of disability globally, type 2 diabetes mellitus (T2DM) has become a major public health concern and increasing global health burden (1). Previous evidence has estimated that the global prevalence of diabetes mellitus in 2019 was 9.3% (463 million individuals), and it will rise to 10.2% by 2030, even to 10.9% by 2045 (2). Therefore, it is necessary to plan effective national prevention and control programs for T2DM management and reducing its disease complications.

The development of T2DM and the occurrence of related complications are chronic processes. Identification of diagnostic biomarkers for glucose metabolism disorder are critical to prevent and control the occurrence and development of T2DM

at the earliest stage. MicroRNAs (miRNAs) are a family of noncoding single-strand RNA molecules (19 to 25 nucleotides) that play an important role both in physiological and pathological pathways by regulating posttranscriptional silencing of target genes (3,4). Several previous studies have showed the different expression levels of circulating miRNAs that have been identified to associate with T2DM and related metabolic diseases, such as obesity and insulin resistance (IR) (5-9), and different research indicated specific upregulated/downregulated miRNAs expression in patients with T2DM or related metabolic diseases. In those miRNAs with altered expression, some are regulating glucose and lipid metabolism in liver such as miR-103/107 and miR-122, and miR-375 and miR-126 are promising clinical biomarkers for T2DM (10). After reviewing the original articles and systematic reviews on the relationship between miRNAs and T2DM or related metabolic parameters, combined with the differentially expressed candidate plasma exosome miRNAs in our established discovery study, miR-126 and miR-122 were screened to be further discussed since they have been widely studied in recent years.

miR-126 and miR-122 has been proposed to play a central role in the regulation of the blood glucose metabolism and the T2DM development (4,11-13). For instance, the plasma miRNA profiles in patients with T2DM revealed dysregulated endothelial miR-126 (6), which could regulate the glucose homeostasis through its target insulin receptor substrate (14). Moreover, animal experiments showed that the fasting blood glucose (FBG) level increased significantly after the birth in the mouse with miR-126 knockdown compared with the wild-type mouse (15). In addition, a prior study suggested that miR-122-5p expression was associated with homeostasis model assessment of insulin resistance (HOMA-IR) index and could predict the presence of IR (a determinant underlying the pathophysiology of T2DM) in adolescents with obesity (16). Although increasing studies have been performed to examine the potential associations of miR-126 and miR-122 expression with T2DM and related glucose metabolism parameters, inconsistent results of existing studies remained. For example, evidence has shown a lower expression level of miR-126 in prevalent T2DM compared with healthy controls (6,11,17), whereas one recent study published in 2021 indicated that miR-126-3p was positively associated with T2DM risk and higher FBG level (18). Therefore, this meta-analysis systematically and quantitatively evaluated the relationship between circulating miR-126 and miR-122 expression levels and the risks of T2DM as well as related glucose metabolism parameters.

Materials and methods

Search strategy. The present study was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline (PRISMA 2020 statement) (<http://www.prisma-statement.org/>). A literature search strategy was developed according to the four elements of the study question (participants, intervention, comparison and outcome) and the study design. PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Embase (<https://www.embase.com>), Web of Science (<https://clarivate.com/webofscience-group/solutions/web-of-science/>), Cochrane Library databases (<https://www.cochranelibrary.com/>) and Chinese National

Knowledge Infrastructure (CNKI, <https://www.cnki.net/>) electronic databases were used to identify eligible original articles published up to May 3, 2022. In addition, the Chinese Biomedical Literatures database (CBM, <http://www.sinomed.ac.cn/index.jsp>), Wanfang Digital Periodicals (<https://www.wanfangdata.com.cn/index.html>), and Chinese Science and Technology Periodicals database (VIP, <http://qikan.cqvip.com/>) were also used to identify additional records (3 studies). The search terms used in these databases are presented in Table SI. Eligible original studies include those published in English or Chinese and those conducted on humans.

Study selection, quality assessment and data extraction.

The selection process of the studies, quality assessment process, and data extraction from the included studies were conducted by two authors (YH and YL) independently in the current meta-analysis. Moreover, controversies regarding the eligibility of the paper were solved through discussion by these two authors (YH and YL), rather than adjudication by a third author. Papers meeting the following criteria were potentially eligible: i) case-control studies or cohort studies investigating the relationship between circulating miR-126 and miR-122 level and the T2DM risk or the correlation with FBG/HOMA-IR index; ii) cross-sectional study with a clear case group and healthy controls at the data analysis stage; iii) study outcomes including T2DM and its complications, obesity, IR [with results expressed as relative ratio (RR), odds ratio (OR), or hazard ratio (HR) and 95% confidence interval (CI)], FBG level and HOMA-IR index [with results expressed as correlation coefficient (r)]; iv) the quality score of the studies assessed by the Newcastle Ottawa Scale (NOS) was at least 6. The excluded criteria were: i) duplication of studies (repeating data that were already reported by other included articles), including articles published by the same authors in different years using the same data; ii) articles were letters, comments, reviews, chapters or conference abstracts only; iii) study outcomes were other diseases which were not associated with diabetes or its complications; iv) articles where the required data was not available or the effect estimates were abnormal; v) studies with the NOS score less than 6 (low-quality).

NOS was used to assess the quality of the included studies, which included selection, comparability and outcome of three categories, with a full score of 9 stars (a maximum of one star for items within the selection and outcome categories, but a maximum of two stars for the items within the comparability category) (19). Furthermore, the following information was extracted from the selected studies by two authors (YH and YL) independently: First author; publication year; study type; study country; sample size and average age of study subjects; definitions and diagnostic criteria of T2DM and related metabolic diseases; assessment of circulating miR-126 and miR-122; the OR/RR/HR and 95% CI of circulating miR-126 related to T2DM; the correlation coefficient (r, 95% CI) of circulating miR-126 and miR-122 with FBG or HOMA-IR index; and covariates of the adjusted model. If there were multiple adjusted models in an original study, the relevant data in the model with the most adjusted covariates were extracted.

Statistical analysis. This meta-analysis aimed to examine the relationship of miR-126 and miR-122 expression level

with T2DM risk, in which effect estimates were expressed as OR (case-control studies), RR or HR (cohort studies). HR and RR were roughly considered equivalent to OR (20). For the effect estimate on T2DM when the independent variable was not changed by one unit, it has been uniformly converted as the independent variable increased by one unit [$OR_{convert} = \exp(\ln(OR_{original}) / \text{original unit change} \times 1\text{-unit change})$]. The method recommended by Hamling *et al* (21) was used to convert effect estimates when the reference group of miR-126 or miR-122 used in the present study was not the lowest level. The random effect model was used to estimate the OR (95% CI) of the included studies (22), and captured differences between the statistical parameters across studies by introducing study-specific effects in the model (23). In addition, the correlation coefficient (r , 95% CI) was assessed between miR-126 and miR-122 expression and FBG level as well as HOMA-IR index, and the corresponding effect estimates expressed as r (95% CI). The r extracted from the selected studies is converted to Fisher's Z value and standard Error (SE) [$ZCOR = 0.5 \times \ln(1+r)/(1-r)$; $SE = 1/\sqrt{n-3}$] (24), then merged and converted to r value (25), and the data were pooled with the random effect model based on the inverse variance method.

Heterogeneity among the included studies was assessed by the Q test and I^2 statistic that describes the proportion attributed to heterogeneity in total variation in study estimates ($I^2 < 50\%$ and $P > 0.05$ were considered as no heterogeneity) (26,27). In addition, subgroup analyses were conducted to examine the potential sources of heterogeneity by sample size (< 100 vs. ≥ 100), source of participants (Asia, Africa, Europe, North America, South America, Oceania), average age of subjects (< 60 vs. ≥ 60 ; < 30 vs. ≥ 30) and study types (descriptive, analytical or experimental studies). Sensitivity analyses were performed to examine the influence of individual studies on the pooled estimates by excluding one study at a time (28). Potential publication bias was assessed by the Begg's funnel plot and Egger's tests, and it was considered as no publication bias if $P > 0.05$ (29,30). All statistical analyses were performed using Stata version 13.1 software (Stata Corp LLC), and R software (version 3.6.1; R Development Core Team).

Results

Literature search and characteristics of included studies. A total of 1717 relevant studies for miR-126 and miR-122 were searched in the aforementioned 8 databases. After removing duplicates, screening the title/abstract, and assessing the full-text article, 46 studies were included in the final analyses about the relationships of circulating miR-126 and miR-122 level with T2DM risk, FBG level and HOMA-IR index (Fig. 1; flowchart for study selection). The NOS scores of the included studies are presented in Table SII, and the scores of all studies were at least 6.

The characteristics of the included studies on the relationship of circulating miR-126 and miR-122 expression levels with T2DM risks, of which the first 7 studies were about miR-126 expression and the risk of T2DM, and the last 3 studies were about miR-122 expression and the risk of T2DM are presented in Table I. Of the 7 studies about miR-126 with the risk of T2DM, 4 were conducted in Asia (2 in Kingdom of Bahrain

and 2 in China), 2 were performed in Europe (1 in Italy and 1 in Sweden) and 1 was in Africa (the Republic of South Africa). The average age of the participants was > 45 years. The sample size of the studies was not less than 100 except for two study in Asia (5,31). Of the 3 studies about miR-122 with the risk of T2DM, 1 was conducted in Asia (China), 1 was performed in Europe (Italy) and 1 was in North America (USA). The average age of the participants was > 50 years. And the sample size of the studies was not less than 100. In addition, the characteristics of the included studies involving correlation of circulating miR-126 and miR-122 expression with FBG level and HOMA-IR index are revealed in Table SIII. Of the 38 studies, 21 were conducted in Asia, 6 in Europe, 5 in North America, 4 in Africa, 1 in South America and 1 in Oceania. In addition, 5 of the studies involved subjects younger than 18 and nearly half of the studies (18/38) had sample sizes of less than 100. Similarly, as revealed in Table SII, all studies on relationship of miR-126 and miR-122 with T2DM-related metabolic parameters were of high quality (with NOS scores ranging from 6 to 9).

Association of circulating miR-126 and miR-122 with T2DM. When 7 studies involving a total of 2,570 participants (484 T2DM cases) were included in the meta-analysis for association of miR-126 with T2DM risk (5,6,11,17,18,31,32), the pooled result showed there was negative association between the expression level of miR-126 and T2DM risk, but did not reach statistical significance (OR: 0.85, 95% CI: 0.67-1.08; Fig. S1). And significant heterogeneity was observed between these studies ($I^2 = 99.3\%$, $P < 0.001$). Besides, in order to detect potential sources of heterogeneity between these studies, subgroup analyses (Table SIV) were performed, which revealed that heterogeneity between these 7 studies was not attributable to study source, study sample size, average age of study subjects, or study types. However, after the exclusion of the 2 cross-sectional studies (18,32), the pooled results of the remaining 5 analytical epidemiological studies (4 case-control studies and 1 cohort study) showed that the association of miR-126 expression level with T2DM risk had a significant negative association (OR=0.73, 95% CI: 0.55-0.96; Fig. 2), and the heterogeneity was decreased to 55.3% ($P = 0.107$) in studies with sample size more than 100 (Table SV). In addition, there was no evidence of publication bias with either Egger's test ($P = 0.731$, Table SVI) or Begg's funnel plot ($P = 1.000$; Fig. S2). Sensitivity analyses demonstrated that the exclusion of one study conducted in China (11) had significant effect on the current pooled results.

For the association of miR-122 with T2DM, there are only 3 relevant studies to date (12,33,34). The Bruneck study (followed up over up to 15 years) found per one standard deviation (SD) increase of log miR-122 was obviously associated with higher T2DM risk in the multivariable model (RR=1.37, 95% CI: 1.03-1.82, $P = 0.021$) (12). Another study conducted in China indicated that miR-122-5p was linked to increased T2DM risk after adjustment for important covariates (OR=1.36, 95% CI: 1.14-1.62) (34). However, the study of Ezaz *et al* (33), revealed that there was no significant association between miR-122 expression and diabetes in patients with non-alcoholic fatty liver disease ($\beta = 0.293$, $P = 0.1$). More future studies are needed to provide related evidence.

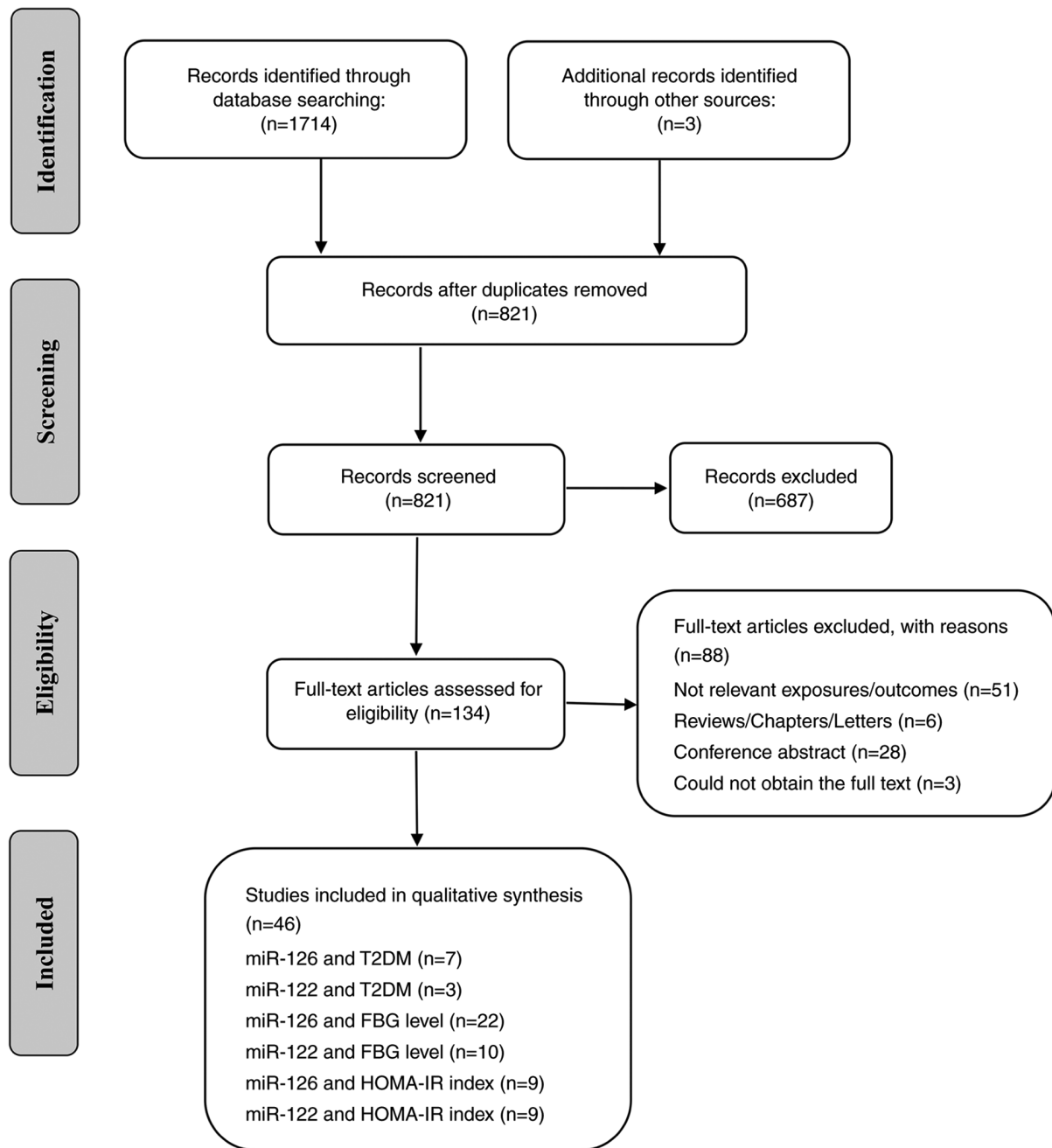


Figure 1. Flowchart for study selection. After removing duplicates, screening the title/abstract, and assessing the full-text article, 46 studies were included in the final meta-analyses.

Correlation between circulating miR-126 and miR-122 and FBG level. A total of 22 studies involving a total of 3,903 participants were included in the meta-analysis for correlation of miR-126 with FBG level (4,8,17,18,35-52). The pooled result revealed significant inverse correlation between miR-126 expression and FBG level with the random effect model ($r=-0.26$, 95% CI: -0.42, -0.10; Fig. 3A). However, significant heterogeneity was observed between these studies ($I^2=97.92\%$, $P<0.001$), but there was no evidence of publication bias with either Egger's test ($P=0.067$, Table SVI) or Begg's funnel plot (Fig. S3A). Subgroup analyses (Table SVII) were conducted to examine the potential sources of heterogeneity, which showed that significant correlations were still observed in the Asian and European studies, and the heterogeneity was

decreased to 53.51% ($P=0.08$) in European studies. Moreover, no heterogeneity was observed in 2 descriptive studies or 2 experimental studies. The heterogeneity may be attributed to different study source and study types of included studies.

In addition, 10 studies involving a total of 1,388 participants were included in the meta-analysis for correlation of miR-122 with FBG level (13,51,53-60), and the pooled result demonstrated significant positive correlation between miR-122 expression and FBG level with the random effect model ($r=0.34$, 95% CI: 0.20, 0.48; Fig. 3B). However, significant heterogeneity was observed between these studies ($I^2=92.01\%$, $P<0.001$). Besides, the Begg's funnel plot shows obvious asymmetry which suggested the presence of a potential publication bias (Fig. S3B), and that was also suggested by the Egger's

Table I. Characteristics of the included studies for association of miR-126 and miR-122 with T2DM risk.

First Author (year)	Country	Sample, n (male/female)	Age, years	Diagnosis and assessment of T2DM	Biological Sample	miRNAs assessment	Adjusted variables	(Refs.)
Zhang (2015)	China	40 (22/18)	59.23±10.14	FPG ≥7.0 mmol/L or 2 h PG ≥11.1 mmol/L in	Plasma samples	miR-126 RT-qPCR	Univariate logistic regression. analyses	(5)
Zampetaki (2010)	Italy	160 (60/100)	40 to 79 years old 66.3±8.9	OGTT WHO criteria	Plasma samples	miR-126 qPCR	Adjusted for age, sex, social status, Fam-TD, BMI, waist-to-hip ratio, smoking status, alcohol consumption, physical activity, and hs-CRP.	(6)
Liu (2014)	China	298 (145/153)	48.58±6.94	World Health Organization criteria	Serum samples	miR-126 RT-qPCR	Adjusted for age, gender, BMI and some biochemical indicators.	(11)
Al-Kafaji (2016)	Kingdom of Bahrain	102 (49/53)	59.06±8.34	World Health Organization criteria	Plasma	miR-126 RT-qPCR	Adjusted for age, gender, BMI and BP, FG and HbA1c, triglyceride, and LDL	(17)
Weale (2021)	The Republic of South Africa	1066 (303/763)	46.36±15.41	WHO criteria	Whole blood	miR-126 RT-qPCR	Included age, sex, BMI, SBP, triglycerides, HDL-C and LDL-C.	(18)
Al-Kafaji (2017)	Kingdom of Bahrain	90 (44/46)	57.00±10.44	World Health Organization criteria	Plasma	miR-126 RT-qPCR	Multivariate logistic regression. analysis	(31)
Wang (2014)	Sweden	152 (83/69)	55.76±5.80	FPG ≥7.0 mmol/L and/or a 2-h PG in the OGTT of	Plasma samples	miR-126 RT-PCR	Adjusted for sex, age, WC, Fam-TD and sedentary lifestyle.	(32)
Willeit (2017)	Italy	910	63±11	1997 American Diabetes Association criteria	Serum samples	miR-122 RT-qPCR	Adjusted for age, sex, socioeconomic status, smoking, physical activity, and alcohol consumption.	(12)
Ezaz (2020)	USA	132 (81/51)	50.6	-	Serum samples	miR-122 RT-qPCR	Univariate logistic regression. analyses	(33)
Nie (2022)	China	188 (82/106)	64.45±6.97	2020 American Diabetes Association criteria	Plasma samples	miR-122 RT-qPCR	Adjusted for age, sex, BMI, smoking status, drinking status, regular exercise, education and. Fam-TD	(34)

T2DM, type 2 diabetes mellitus; RT-qPCR, reverse transcription quantitative polymerase chain reaction; BMI, body mass index; WC, waist circumference; BP, blood pressure; SBP, systolic blood pressure; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein protein; HDL-C, high-density lipoprotein protein; Fam-TD, family history of type 2 diabetes; OGTT, oral glucose tolerance test; FPG, fasting plasma glucose; hs-CRP, high-sensitivity C-reactive protein.

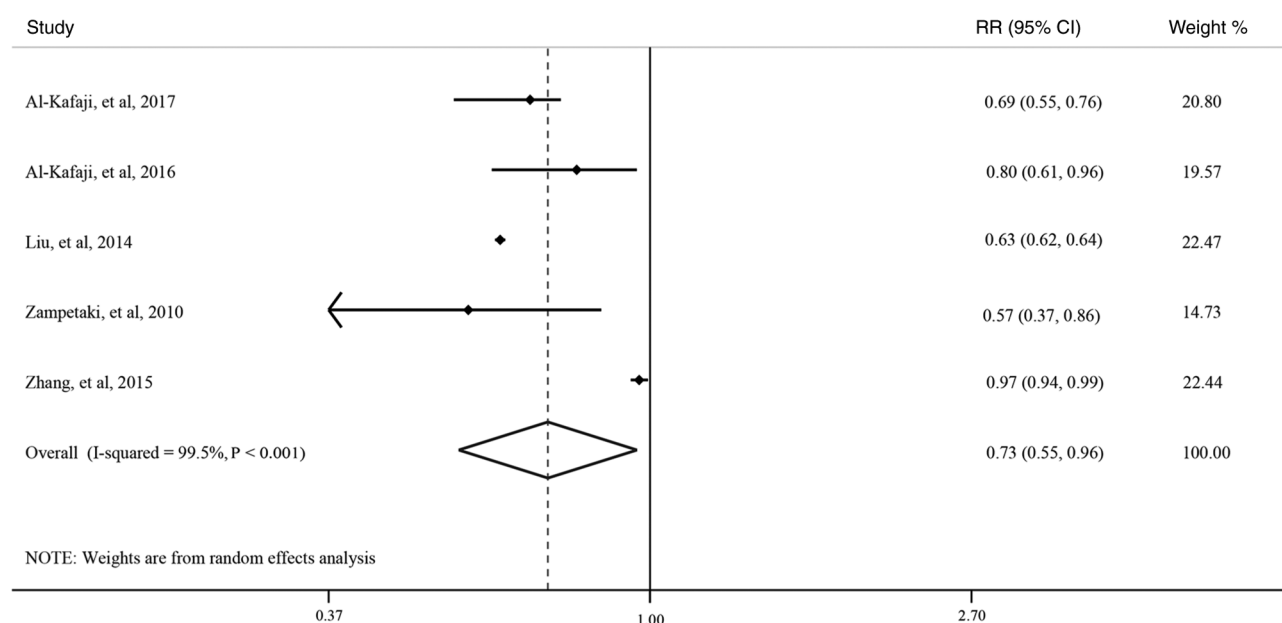


Figure 2. The association of miR-126 expression with T2DM risk. A total of five analytical epidemiological studies were included in the meta-analysis for association of miR-126 expression with T2DM risk. The pooled estimates were obtained using a random-effects model, the solid line represents the position of the '1' (the reference) on the x-axis, and the dotted line represents the position of the pooled relative risk on the x-axis. miR, microRNA; T2DM, type 2 diabetes mellitus.

test ($P=0.001$, Table SVI). Subgroup analyses (Table SVIII) indicated that significant correlation persisted in the Asian and African studies, and no heterogeneity was observed in studies with sample size less than 100 and moderate heterogeneity was observed in studies with participants younger than 30 years. The heterogeneity may be attributed to different sample size of included studies and the average age of included subjects.

Correlation between circulating miR-126 and miR-122 and HOMA-IR index. A total of 9 studies involving a total of 1,384 subjects were included in the meta-analysis for correlation of miR-126 with HOMA-IR index (4,32,37,51,61-65). The pooled result revealed significant inverse correlation between miR-126 expression and HOMA-IR index with the random effect model ($r=-0.28$, 95% CI: -0.52, -0.05; Fig. 4A). However, significant heterogeneity was observed between these studies ($I^2=97.10\%$, $P<0.001$), and heterogeneity was still significant when the most influential study was excluded (32) ($r=-0.35$, 95% CI: -0.57, -0.14; $I^2=96.22\%$, $P<0.001$). Furthermore, there was no evidence of publication bias with the Egger's test ($P=0.098$; Table SVI), and the Begg's funnel plot suggested roughly symmetry (Fig. S3C). On subgroup analyses (Table SIX), significant correlations persisted in the Asian and African studies, as well as in participants with age ≥ 60 years, and no heterogeneity was observed in studies with participants aged no less than 60 years. The heterogeneity may be due to the average age of subjects in different included study.

A total of 1,190 subjects were involved in the 9 included studies in the meta-analysis for correlation of miR-122 expression with HOMA-IR index (9,16,51,53-56,58,65), and positive correlation for miR-122 and HOMA-IR index was found in the pooled result with the random effect model ($r=0.40$, 95% CI: 0.16, 0.64; Fig. 4B). However, significant

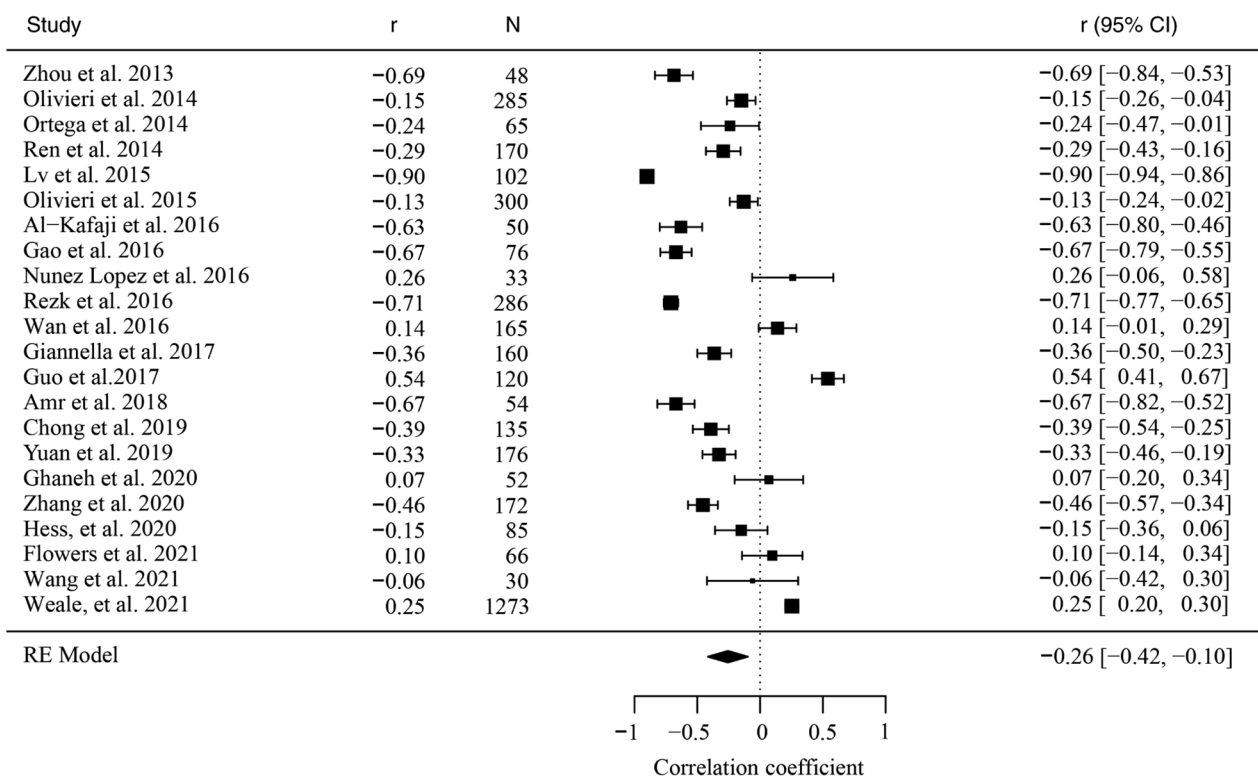
heterogeneity was observed between these studies ($I^2=97.29\%$, $P<0.001$), and heterogeneity was still significant when the most influential study was excluded (9) ($r=0.50$, 95% CI: 0.35, 0.66; $I^2=93.01\%$, $P<0.001$). The Begg's funnel plot revealed asymmetry (Fig. S3D) and there was evidence of publication bias with the Egger's test ($P=0.044$, Table SVI). On subgroup analyses (Table SX), significant correlations persisted in the Asian studies, studies with participants ≥ 100 , as well as in participants with age <30 years, but not in the Oceanian, North American, European studies and those with sample size <100 and aged ≥ 30 years.

Discussion

To the best of our knowledge, original research or reviews on relationship of miRNAs with T2DM risk are abundant, but limited studies have systematically examined the associations of miR-126 and miR-122 expression level with the T2DM risks. Moreover, no study has explored the correlations between miR-126 and miR-122 expression and the FBG level or HOMA-IR index to date. Therefore, this meta-analysis pooled the results of the existing relevant studies and drew quantitative conclusions.

In the present study, negative association was found between circulating miR-126 expression and the T2DM risk, and the association was statistically significant after the exclusion of the 2 cross-sectional studies. Regarding the relationship of miR-126 level with T2DM risk, the results of the current available studies were inconsistent. The study types may partly account for the inconsistent results. For example, no statistically significant association was identified between circulating miR-126 expression and the T2DM risk among the pooled result from 7 studies. However, after the exclusion of the 2 cross-sectional studies (18,32), the pooled result were

A



B

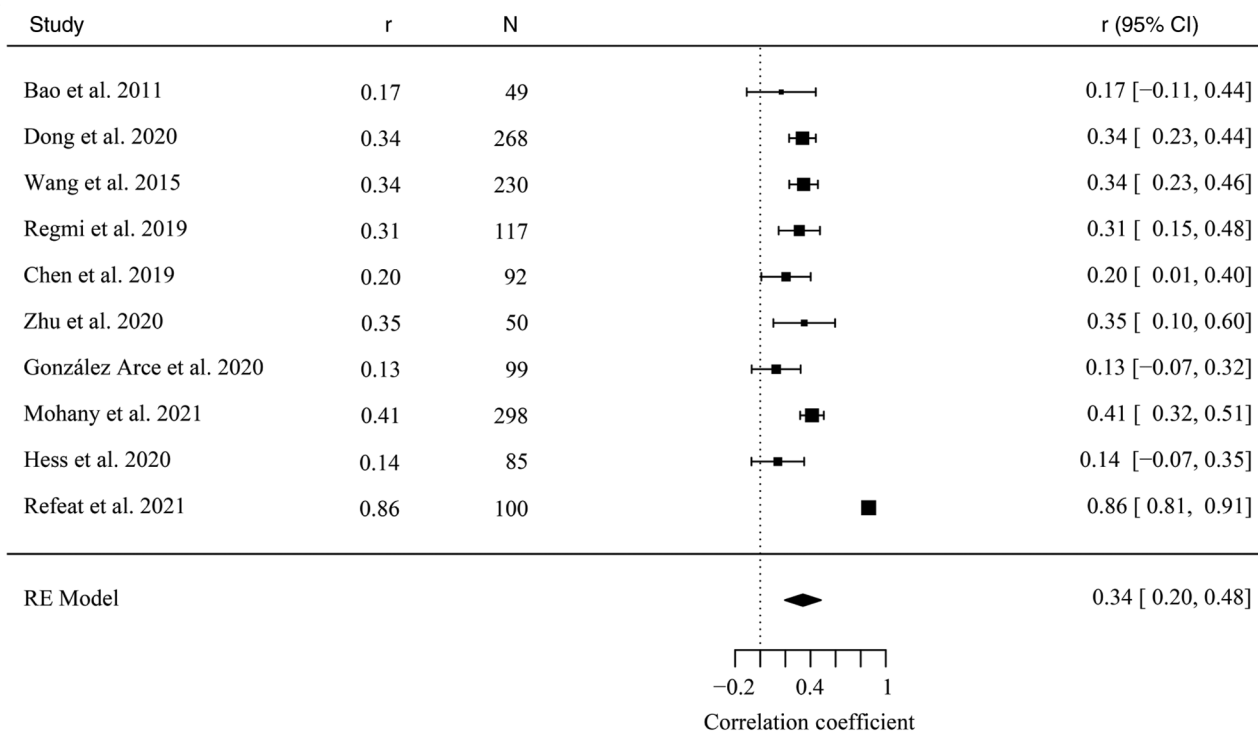


Figure 3. Correlation of miR-126/miR-122 expression with FBG level. (A) 22 studies were included in the meta-analysis for correlation of miR-126 expression with FBG level. (B) 10 studies were included in the meta-analysis for correlation of miR-122 expression with FBG level. The pooled estimates were obtained using a random-effects model, and the dotted line represents the position of the '0' (the reference) on the x-axis. miR, microRNA; FBG, fasting blood glucose; CI, confidence interval.

statistically significant, and the heterogeneity was decreased in studies with sample size more than 100.

Besides, marked differences were observed in miRNA profiles as well as T2DM prevalence across racial and ethnic groups (66,67). For differences of the miRNA profiles among

different ethnic groups, for example, miR-146a and miR-15 were significantly lower in subjects from Mexico compared with that from the US (49). Additionally, for differences in the T2DM prevalence across racial and ethnic groups, for instance, the diagnosed diabetes prevalence among American

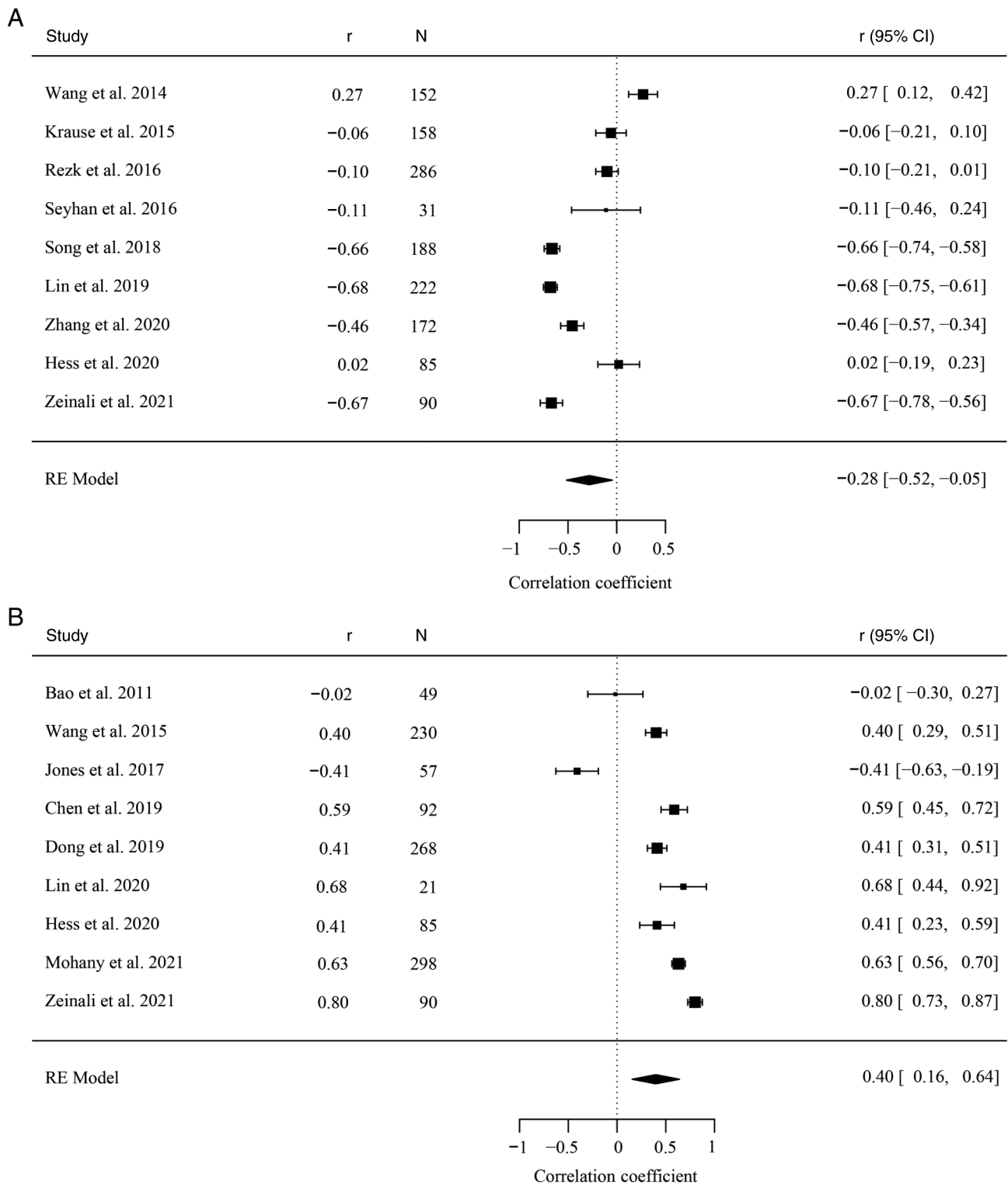


Figure 4. The correlation of miR-126/miR-122 expression with HOMA-IR index. (A) 9 studies were included in the meta-analysis for correlation of miR-126 expression with HOMA-IR index. (B) 9 studies were included in the meta-analysis for correlation of miR-122 expression with HOMA-IR index. The pooled estimates were obtained using a random-effects model, and the dotted line represents the position of the '0' (the reference) on the x-axis. miR, microRNA; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval.

Indians/Alaska Natives is almost twice that of Caucasian Americans in the United States (14.7% vs. 7.5%) (68). In Europe, compared with Caucasian European populations, Latin American, East and Southeast Asian, sub-Saharan African, Middle Eastern and North African, and South Asian populations are 1.3-3.7 times as likely to develop

T2DM (69). Moreover, previous studies have shown that significant association of higher miR-144 expression with T2D risk was observed in Swedes (OR=2.43, P=0.035), but not in Iraqis (P=0.169) (32). Furthermore, strongest association of miR-126-3p with FBG level was observed in Hispanic men, and a moderate correlation was found between miR-192 and

FBG in Black women (66). Therefore, it was hypothesized that ethnicity of the study population may account for the inconsistent results. More studies are needed in the future to support and verify the findings of the current meta-analysis.

Except for the negative association of miR-126 expression with T2DM risk, negative correlations were also found between circulating miR-126 expression and FBG level as well as HOMA-IR index (two important indicators of T2DM) in the present meta-analysis. Some established evidence suggested similar results. For example, the study of Zhang *et al* (70) showed that miR-126 expression level was significantly reduced among the participants with medium or high FBG compared with those with low FBG (both $P < 0.05$). Moreover, one previous study conducted in Italian population with different degrees of glucose condition found that FBG level was significantly associated with the reduced expression level of miR-126-3p ($\beta = -0.286$; $P = 0.003$) (47). Besides, prior studies in China demonstrated that miR-126 expression was low in patients with newly diagnosed T2DM, which may be involved in the development and progression of IR and T2DM (37,63,65,71). These findings indicated that miR-126 could be used as a biomarker of low FBG level and HOMA-IR index, as well as the low risk of the T2DM development. Of course, the development of T2DM may require the intricate interactions of multiple miRNAs, genetics, environment and lifestyle.

Meanwhile, positive correlations were observed between miR-122 expression and FBG level as well as HOMA-IR index in the present meta-analysis, which suggested that miR-122 could be involved in IR and may be used as a potential biomarker of T2DM risk. For the association of miR-122 with T2DM, relevant studies are limited to date. Previous studies from the Bruneck Study and China found that miR-122 was obviously associated with increased T2DM risk ($P < 0.05$) (12,34). Moreover, previous studies showed that miR-122 expression level was significantly increased in patients with T2DM when compared with healthy control, and miR-122 was positively associated with FBG ($P < 0.05$) (13,57,58). Moreover, evidence suggested that elevated circulating miR-122 was an independent risk factor for IR in young adults (OR=3.379 for 1-SD unit increase of miR-122 level, $P < 0.05$) (56), and correlation was also observed in both the general children and those obese ($r = 0.586$, $P < 0.001$; $r = 0.442$, $P = 0.002$, respectively) (54). The finding was also supported by a previous systematic review (72).

Evidence has shown that circulating miRNAs are packaged inside proteins or extracellular vesicles (such as exosomes and microvesicles) to avoid being degraded by RNase (73). Islet endothelial progenitor cells-derived microvesicles miR-126 may sustain revascularization and β -cell function of human pancreatic islets (74). In addition, a previous study indicated that lean mice treated with exosomes transfected with obesity-associated miRNAs mimics (including miR-122) for 4 weeks were glucose intolerant and IR (75). However, there was no study exploring the associations of plasma exosomal miR-126 and miR-122 with T2DM to date. Future studies are needed to be conducted to assess these associations.

Previous studies demonstrated that miRNAs were involved in multiple metabolic pathways, including insulin signaling, adipokine expression, adipogenesis and lipid metabolism. For

the potential mechanisms of miR-126 expression with the metabolic diseases, established epidemiological studies have suggested some pathways (74,76-79). On one hand, abnormal islet β cell function is the basis of dysglycemia and IR. A previous study revealed that miR-126 carried by microvesicles derived from islet endothelial progenitor cells may sustain revascularization and β -cell function of human pancreatic islets (74). On the other hand, endothelial dysfunction commonly occurs in the earliest stages of the diseases and is associated with T2DM (76). Moreover, previous studies have shown that miR-126 was highly enriched in endothelial cells and played a pivotal role in maintaining endothelial homeostasis and vascular integrity through regulating vascular endothelial growth factor, Angiopoietin-1 and vascular cell adhesion protein-1 expression levels (77-79). In addition, for the pathways of miR-122 expression with the metabolic diseases, previous study showed that miR-122 may promote the development and progression of IR directly through inhibiting the IGF-IR/PI3K/AKT pathway (55), which was related to multiple physiological processes including diseases such as diabetes. Moreover, miR-122 directly targets protein-tyrosine phosphatase 1B and regulates the insulin/insulin-like growth factor signaling pathway (80). Besides, miR-122 has also been implicated in glucose homeostasis by indirect effects on AMP-activated kinase and glucose 6-phosphatase, a key regulatory enzyme of hepatic gluconeogenesis (81). Further studies are warranted to explore the potential mechanism.

Several subgroup analyses were conducted to discover the potential sources of the high heterogeneity of the included studies. When the study types were limited to analytical epidemiological studies, moderate heterogeneity was observed for the association between miR-126 and T2DM risk in studies with a sample size of 100 or more. Besides, no heterogeneity was found in North American studies and a moderate heterogeneity was observed in European studies for the correlation of miR-126 with FBG; no heterogeneity was observed in North American and European studies for the correlation of miR-122 with FBG. This may be explained by different sources of limited study subjects and different ethnicity or lifestyle in different countries as well as varied quality levels of included studies. In addition, significant association and no heterogeneity were observed in group with participants less than 100 for the correlation of miR-122 with FBG. For average age, heterogeneity was significantly reduced in participants aged ≥ 60 years for the correlation of miR-126 with HOMA-IR, which may be explained by the fact that metabolic disease was a chronic condition that was highly age-dependent (82). Besides, the high heterogeneity may be explained by the quality of studies or the ethnicity (different countries) of the study population to a certain degree. More numbers of studies with high quality and different ethnicity are needed to explore this association in the future.

There were several limitations to the present meta-analyses that should be considered. Firstly, due to the limitations of the quantity, quality and data extraction of the papers, some studies exploring the association between individual miRNA and T2DM were not included. Secondly, the numbers of included analytical studies are relatively limited in the association of miR-126 or miR-122 expression with T2DM risk. More relevant and available analytical

epidemiological studies are needed in the future to make more definitive conclusions. Thirdly, high heterogeneity was found due to the difference of population demographics from different regions (such as ethnicity, lifestyle), the varied quality of studies, different age of recruited participants and inconsistent covariate adjustment in each study. Fourthly, exposure-response relationship could not conduct in the current meta-analyses due to limited eligible studies and categories of cases. Future studies were encouraged to assess the dose-response relationship between miR-126 and miR-122 expression and T2DM risk as well as related metabolic parameters. Finally, some important factors such as family history of diabetes and dietary intake were not adjusted in some included studies, and it may remain other unmeasured and residual confounders in original studies.

In conclusion, the current meta-analyses suggested that high miR-126 expression was negatively correlated to lower T2DM development risk, FBG level and HOMA-IR index in the general healthy population. Besides, miR-122 expression was related to higher FBG levels and HOMA-IR index in the general healthy population. The findings have notable clinical and public health implications for screening and control of glucose metabolic disorders, IR and T2DM development. However, more multicenter studies with large sample sizes are needed to draw the firm conclusions.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YH and XL conceived and designed the present study. YH and YL carried out literature search, study selection, quality assessment and data extraction. ZhiZ, PL, and YZ confirm the authenticity of all the raw data. YH, YZ and LN performed statistical analysis, and were assisted by ZhiZ and PL. YH, XL and YL wrote the manuscript. JH, WH, ZM, ZheZ and CW interpreted the data and revised the manuscript. The final

version of the publication was written by YH, XL, YL and YZ. XL had primary responsibility for final content. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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